Studying the effects of periconceptional folic acid supplementation

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Summary

Periconceptional folic acid (FA) supplementation has been recommended since two decades to all women to prevent neural tube defects (NTD) in their offspring. Uncertainty remains, however, about the optimal dose and duration of supplementation and about other effects of FA, on the occurrence of congenital anomalies (CA) other than NTD and adverse pregnancy outcomes such as preterm birth, and potential – positive and negative – side-effects. One of the aims of this thesis is to augment the literature to unravel the inconclusive evidence. Part 1 of this thesis presents two studies on the effects of FA, on CA and on pregnancy outcomes, and the design and rationale of a prospective meta-analysis that aims to provide more conclusive evidence on the effects and optimal dose and duration of FA supplementation. This prospective meta-analysis initiative included an RCT located in the Netherlands, which in this thesis will be referred to as FA-Extra. The focus of part 2 is on women's attitudes and willingness to FA supplementation and participation in a FA trial, to gain insight in factors contributing to the inclusion in FA-Extra. In part 3 the experiences and results of trial recruitment and inclusion are presented.

Part I: Folic acid supplementation and congenital anomalies and pregnancy outcomes

Chapter two describes a case-control study on the association between FA and congenital urinary tract and genital anomalies (CUGA). In this study three hypotheses are tested. First, we expected a preventive effect of periconceptional FA supplementation on CUGA. This was only was found cystic kidney, but not for other subtypes or overall CUGA. The second hypothesis, that CUGA are associated with the use of FA antagonists prior to and during pregnancy, was not confirmed either. We were the first to test the third hypothesis, that CUGA are more likely to co-occur with FA-related congenital anomalies (CA) than with non-FA related CA. Infants with multiple congenital anomalies (MCA) with at least one CUGA and no known aetiology were less frequently affected with other FA-related CA compared to MCA cases without CUGA. This hypothesis needs further investigation. Our results suggest no association between FA supplementation and the occurrence of CUGA.

In **chapter three** the association between FA supplementation and preterm birth (<37 weeks of gestation) and small for gestational age (SGA, <5th percentile) babies is studied using data of the Dutch DELIVER cohort. The reported use of folic acid supplements during the third trimester of pregnancy was associated with a reduced risk for preterm birth in this cohort. No association was found for overall FA use, or SGA. Folic acid use during the third trimester might contribute to the prevention of preterm birth. Almost all women in this study who reported FA use in the third trimester, reported use in the periconceptional period too. Our results are also supportive of the hypothesis that continued folic acid use rather than use in late pregnancy only, reduces the risks of preterm birth.

The study protocol in **chapter four** describes the protocol of a prospective meta-analysis that aims to provide more conclusive evidence on the effects and optimal dose and duration of FA supplementation. This prospective meta-analysis initiative included an RCT located in the Netherlands.

Part II: Women's attitudes and willingness towards folic acid supplementation and trial participation

This part focuses on women's attitudes and willingness towards folic acid supplementation and trial participation. An attitude scale to measure women's Attitude towards Periconceptional Vitamin Use (APVU scale) is presented and validated in **chapter five**. The APVU scale is a semantic differential scale and consists of seven 5-point bipolar adjective pairs. Two factors were extracted, a cognitive and an affective scale, which both had high reliability scores. A comparison was made between a version with positive and negative connoted adjectives presented on different sides and a one-direction version. Scores on the one-direction scale version were significantly higher. Construct validity was confirmed with five hypotheses, none of which had to be rejected. These hypotheses included that women who used FA, women who have the intention to use FA, an women who would give the advice to use FA to other women, have higher attitude scores.

Chapter six describes a qualitative study into women's attitude and willingness towards participation in FA-Extra. This study preceded the start of FA-Extra and aimed to get insight into the possible success (inclusion of participants) and factors that contribute to that. All

participants were positive about FA-Extra. The main reason for reserved attitudes to participation in FA-Extra was uncertainty about side-effects and safety of the study medication. Key stimuli for participating were a desire to benefit future women and children or one's own child. Women expressed a need for more information and named partners and general practitioners as key persons to consult before deciding to participate in FA-Extra. Based on that study no major barriers to participation were expected, if safety – especially on possible side-effects – is explained sufficiently.

Part III: Trial recruitment and inclusion

Despite the positive results shown in part II, the inclusion rate of FA-Extra fell short. Several studies were executed to understand the reasons for this undesirable outcome. **Chapter seven** describes the results of three questionnaire studies in different settings (women who received a mass mailing about FA-Extra; women who visited the website of the nine-month fair; and women in the streets of the FA-Extra region), which aimed to gain insight in the reach of the recruitment strategy of FA-Extra, and assessed in which (sub)populations and in what stage of the decision making process improvement could be achieved, in order to benefit future preconception and prenatal trial initiatives. The awareness about FA-Extra was low. Currently trying to get pregnant and more positive attitude scores were predictive of a willingness to participate in FA-Extra. A small minority (10%) of the women receiving the mass mailing reported negative feelings about the mailing. Many women would discuss participation to FA-Extra with their partner and others, and would search the internet for information about the trial, which is similar to the results in Chapter six. The recruitment strategy should focus on the first stage of the innovation-decision process (knowledge) to increase awareness.

In **Chapter eight** the recruitment strategy and the results of the trial recruitment and inclusion are presented. Sixty-nine community pharmacies (CP) joined FA-Extra, and in 60 of them a total of 335 participants were included in FA-Extra. Of these women, 155 became pregnant. Information on the outcomes of pregnancy will be collected until one year after birth (mid 2015). The most mentioned sources where the women who signed-up for participation first heard or read about the trial were the letter by the CP (mass mailing), the CP itself and the trial's website that had been found via online search engines.

The results of these chapters show that recruitment and inclusion of participants via our chosen strategy is possible, but less effective than expected. A mailing of leaflets and invitations from the CP's led to a reasonable base response rate in the first year of the recruitment and only a minority of the women who received this mailing reported negative feelings about receiving it. To have achieved the number of participants initially aimed for (5200) this response rate would have had to be increased, and for this additional recruitment strategies would have been necessary and, in addition, a wider range of the recruitment and longer inclusion period .

Concluding remarks

Given the difficulties in executing them, it is not likely that future RCTs will provide definite answers on the effects of periconceptional and prenatal FA supplementation in a reasonable period of time, results from less optimal study designs should – although interpreted with caution - be acknowledged for their value to the accumulating evidence. Recommendations in health care practice guidelines and public health policy are based mainly on evidence from RCTs. Health care practice –in specific preconception care – and public health campaigns should however benefit from other research methods in the prevention of congenital anomalies and adverse pregnancy outcomes.